REMARKS

1. STATUS OF THE CLAIMS

Claim 123 has been amended for further clarity by reciting in step d) that the first anionic BAP-glycan conjugate has "from 1 to 2 negative charges per molecule." Antecedent basis for this term is in step c) of Claim 123.

Claim 124 has been amended to recite in step f) that the second anionic BAP-glycan conjugate has "from 1 to 2 negative charges per molecule." Antecedent basis for this term is in step e) of Claim 124.

Claims 130-131 have been amended for further clarity to recite that the first anionic glycan and the first and second desialylated anionic glycans contain from 1 to 4 negative charges "per molecule."

Claim 135 has been amended to recite that the specific binding of the antibody to a carboxylated glycans "is not reduced by a carboxylate-neutralized glycan." Support is found in the Specification in, for example, the paragraph bridging pages 56-57 that teaches:

> "In one preferred embodiment, the binding of the carboxylated glycan-specific antibody to the carboxylated glycan is reduced by a carboxylated glycan, and the binding is not reduced by a carboxylate-neutralized glycan. The term "not reduced" when in reference to the binding of an antibody to a carboxylated glycan means that the quantity of binding of the antibody to the carboxylated glycan is not reduced by a statistically significant amount using any art-accepted statistical method of analysis. The term "carboxylate-neutralized glycan" refers to a glycan in which the anionic charge on a carboxylate group is neutralized either reversibly or irreversibly. Methods for neutralizing carboxylate charges are known in the art and exemplified herein. For example, reversible neutralization may be achieved by alkylamidation such as by using methylamine, ethylamine, *etc.*, while irreversible neutralization may be achieved by alkylesterification such as by using methylamine, ethylamine, propylamine, *etc.* (Example 2). For example, data herein demonstrates that binding of mAbGB3.1 to immobilized BSA neoglycoproteins could be blocked by *asialo*-COO$^-$glycopeptides in solution, but not by *asialo*-CONHMe-glycopeptides (Figure 2, Panel A)."

Additional support is in Example 2, page 85-86 that shows an exemplary method of irreversible neutralization by alkylesterification. More support is in the paragraph bridging pages 87-88 and Figure 33, which demonstrates that screening of hybridomas showed differential reactivity to *asialo*-COO$^-$glycopeptides versus *asialo*-CONHMe-glycopeptides. Yet more support is found in

Example 25, page 121, Figure 22 and its description in the paragraph bridging pages 15-16, which demonstrate that soluble COO^- glycopeptides, but not CONHMe-species, blocked binding of soluble RAGE (sRAGE) to the exemplary mAbGB3.1.

Claim 136 has been amended by canceling reference to cancer to avoid potential duplication of new Claim 160, and by reciting that inflammation is "in a tissue comprising endothelial cells that express said carboxylated glycan." Support is in the Specification on, for example, page 78, lines 1-5, Figure 29 description on page 18, lines 7-8 and Example 33, page 130, line 22 to page 131, line 9, which discusses histological analysis in an *in vivo* mouse model of inflammation.

Claims 144-150 have been withdrawn as being drawn to a nonelected invention.

Claim 151 has been added to recite that the "antibody does not specifically bind to one or more acid selected from the group consisting of glucuronic acid, galacturonic acid, sialic acid, lactic acid, pyruvic acid, and uronic acid." Support is in the Specification on, for example, page 57, lines 14-21, Example 11, Figure 2, panel C.

New Claim 152 has been added to recite that the "antibody does not specifically bind to one or more sulfated glycan selected from the group consisting of thyroglobulin and neural cell adhesion molecule." This supported by the Specification on, for example, page 57, lines 22-27, and Example 3.

Newly added Claim 153 recites that the "antibody does not specifically bind to one or more glycosaminoglycan selected from the group consisting of chondrosamine, chondroitin sulfate, chondroitin sulfate tetramer, chondroitin sulfate octamer, hyaluronic acid tetramer, hyaluronic acid octamer, heparin, and heparin sulfate." Support is in the Specification on, for example, the paragraph bridging pages 57-58, and Example 3.

Claim 154 recites that the "antibody does not specifically bind to one or more phosphorylated sugar selected from the group consisting of glucose-1-phosphate, glucose-6-phosphate, mannose-6-phosphate, and galactose-6-phosphate." This is supported by the Specification on, for example, page 58, lines 5-10 and Example 10.

New Claim 155 recites that the "antibody does not specifically bind to one or more sulfated sugar selected from the group consisting of glucose-6-sulfate and galactose-6-sulfate." Support may be found in the Specification at, for example, page 58, lines 5-10 and Example 10.

Newly added Claim 156 recites that the "carboxylated glycan binds to a molecule comprising one or more of S100A8, S100A9, S10012, amphoterin, annexin I, and amino acids 1 to 12 of annexin I." Support is the Specification at, for example, page 8, lines 9-21 and Example 14, page 104-107 which teaches the specifically recited carboxylated glycans.

New claim 157 recites "identifying said test agent as reducing adherence of leukocyte cells to endothelial cells that express said carboxylated glycan. Support is in the Specification at, for example, the legend of Figure 10 on page 12, lines 17-25, the legend of Figure 17 on page 15, the paragraph bridging pages 8-9, paragraph bridging pages 55-56, page 77, lines 1-16, Example 9 beginning on page 95, and Example 10 on page 98, lines 17-27.

Claim 158 recites "identifying said test agent as reducing transmigration of leukocyte cells in endothelial tissue that comprises endothelial cells expressing said carboxylated glycan." Support is in the Specification at, for example, page 56, lines 11-17, page 98, line 27 to page 99, line 2.

New Claim 159 recites "identifying said test agent as reducing extravasation of leukocytes cells in endothelial tissue that comprises endothelial cells expressing said carboxylated glycan." Support is found in the Specification in, for example, the paragraph bridging pages 68-69, in Example 10 beginning on page 96, and in Example 34 beginning on page 129.

Newly added Claim 160 recites "identifying said test agent as reducing growth of cancer cells that express said carboxylated glycan." This is supported by the Specification at, for example, Figure 23 legend, page 16, lines 6-21, page 78, lines 6-10, and Example 28, page 123, lines 14-21.

New claim 161 recites that the "carboxylated glycan that is expressed by said cancer cells binds to a molecule comprising one or more of S100A8, S100A9, S10012, amphoterin, annexin I, and amino acids 1 to 12 of annexin I." Support is the Specification at, for example, page 8, lines 9-21 and Example 14, page 104-107 which teaches the specifically recited carboxylated glycans.

Newly added claim 162 recites "identifying said test agent as reducing growth of neuron cells that express said carboxylated glycan." Support is in the Specification in, for example, the description of Figures 25-27, from page 17, line 6 to page 18, line 4, and Example 33 beginning

on page 127, which discusses the effects of exemplary agents in neuron outgrowth assays, as also shown in Figures 25-27.

New Claim 163 recites that the isolated first anionic BAP-glycan conjugate in step d) has "1 negative charge per molecule." Support is in the Specification on page 49, lines 20-27 which say that the first anionic BAP-glycan conjugate has "from 1 to 2 negative charges per molecule, more preferably having 1 negative charge per molecule.

Newly added Claim 164 recites that the isolated second anionic BAP-glycan conjugate in step f) "has 1 negative charge per molecule." This is supported by the Specification on page 52, lines 7-14 which teach that the carboxylated glycans that are enriched by exoglycosidase treatment have "from 1 to 2, more preferably 1, negative charges per molecule."

New Claims 165-166 recite that the first and second desialylated anionic glycans have "from 1 to 3" negative charges per molecule. Support is on page 52, line 30 to page 53, line 2 and page 53, lines 18-21 which teach isolating a first and second "anionic glycan containing from 1 to 5, more preferably from 1 to 4, and most preferably from 1 to 3 negative charges."

Claim amendments were made to describe particular embodiments of the invention, notwithstanding Applicant's belief that the cancelled and unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, but rather for the purpose of furthering Applicant's business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG).[1]

2. ELECTION

Applicant notes that instant Claims 123-143 (Group I) were examined on the merits and that Claims 144-150 were withdrawn from consideration as being drawn to a non-elected invention.[2]

Upon allowance of a generic claim in elected Group I (Claims 123-143),[3] Applicant respectfully requests rejoinder (a) of claims to additional species, including currently withdrawn

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1 65 Fed. Reg. 54603 (September 8, 2000).

2 Office Action, page 2, items 1-3.

3 Group I consisted of original Claims 1, 6, 9, 29 and 32 per the Examiner's Office communication mailed 3/15/2007. In the "Amendment and Response" mailed on 6/15/07, Applicant elected Group I by re-writing the elected claims as Claims 123-150.

Claims 144-150, and (b) of Claims 33-35 (Group III), when written in dependent form or that otherwise include all the limitations of an allowed generic claim, as provided by 37 CFR § 1.141.

3. REJECTION OF CLAIMS 142 AND 143 UNDER 35 U.S.C. § 112, FIRST PARAGARPH (ENABLEMENT)

The Examiner rejected Claims 142 and 143 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement.[4] Applicant respectfully disagrees because the Specification provides sufficient guidance to one of ordinary skill in the art to make the recited monoclonal IgG antibodies.

The Examiner is respectfully reminded that "[p]atents . . . are written to enable those skilled in the art to practice the invention."[5] The Examiner argued that the recited antibodies mAbEE4.1, mAbGB3.1, mAbB2.6, or mAbEH2.7 "must be readily available or obtainable by a repeatable method set forth in the specification, **or** otherwise readily available to the public."[6] Regarding the Specification's teachings, the Examiner took the position that "the process disclosed in the specification does not appear to be repeatable, it is not clear that the invention will work with commonly available material and it is not apparent if the biological material are both known and readily available to the public."[7] This position is contradicted by the Specification's teachings in Example 3, beginning on page 86, regarding the type of immunized mouse (BALB/c), immunogen used (streptavidin neoglycoconjugates), and screening the hybridomas for binding to immobilized carboxylated glycans (*asialo*-COO^- glycopeptides and *asialo*-CONHMe-glycopeptides). Applicant avers that the above disclosure is sufficient for one of ordinary skill in the art to make and use the recited antibodies mAbEE4.1, mAbGB3.1, mAbB2.6, or mAbEH2.7.

Nonetheless, Applicant will deposit the hybridomas that produce the recited mAbEE4.1, mAbGB3.1, mAbB2.6, or mAbEH2.7 during pendency (*i.e.*, on or before payment of the issue fee)[8] at the American Type Culture Collection (ATCC) under the terms of the Budapest Treaty

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4 Office Action, page 2, item 5.

5 (Emphasis added) W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983), cert. denied, 105 S. Ct. 172 (1984).

6 (Emphasis added) Office Action, page 3, item 6.

7 Office Action, page 3, item 7.

8 37 C.F.R. §1.804, MPEP §2406.

as requested by the Examiner.[9] Applicant submits the enclosed Statement of Biological Culture Deposit Under 37 C.F.R § 1.808 to certify that the deposit will meet the criteria set forth in 37 C.F.R. § 1.801-1.809 and MPEP § 2402-2411.05.

In view of the above, withdrawal of the rejection of Claims 142 and 143 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement is respectfully requested. Applicant also avers that new Claims 151-155 are enabled since the Specification teaches how to make and use antibodies of the recited specificity.

4. REJECTION OF CLAIM 136 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The Examiner rejected Claim 136 under 35 U.S.C. § 112, first paragraph, for alleged inadequate enablement.[10] Applicant respectfully traverses because the specification provides ample teaching of how to make and use the recited method steps of Claim 136.

Prior to discussing the substance of the rejection, Applicant notes that the Examiner recognized that the "the disclosure provides guidance for the identification of an agent which reduces **inflammation** or cancer cell growth related to the binding of the proteins annexin I, S100A8/A9 and amphoterin."[11] Applicant notes that newly added Claims 156 and 161 recite that the "carboxylated glycan binds to a molecule comprising one or more of S100A8, S100A9, S10012, amphoterin, annexin I, and amino acids 1 to 12 of annexin I." In view of the Examiner's statement, new Claims 156 and 161 are enabled.

The rejection is further discussed below with reference to amended Claim 136 and newly added Claims 156-162.

A. Leukocyte Cells And Inflammation

Regarding Claim 136, the Examiner argued that "the disclosure does not provide any guidance or working examples to direct one to the development of a screening method that would identify any test agent that reduces inflammation."[12] This is incorrect since the Specification discloses not just one, but **two** exemplary mouse animal models.

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9 Office Action, page 3, item 9.
10 Office Action, page 4, item 10.
11 (Emphasis added) Office Action, page 5, 2nd paragraph.
12 Office Action, page 5, 2nd paragraph.

The first animal model is of zymosan-induced acute peritoneal inflammation described in Example 10, beginning on page 96. The Specification teaches that injection of the exemplary agent antibody mAbGC3.1 caused a "substantial reduction" in the appearance of Gr-1^{high} neutrophils and Gr-1^{low} / Mac-1^{high} monocytes in the inflamed peritoneum.[13]

The second animal model is of colitis and Crohn's disease described in Example 34, beginning on page 34. Data in Example 34 show that the exemplary agent antibody mAbGB3.1 reduced inflammation as shown by a reduction in weight loss (Figure 28), diarrhea, death, and severe colonic inflammation as measured by histological analysis of the colon (Figure 29).

One of ordinary skill in the art thus understands that these exemplary animal models may be used by substituting an test agent of interest with the exemplary antibody mAbGB3.1. This is sufficient for enablement of amended Claim 136.

Also regarding Claim 136, the Examiner referred to the Specification's teachings on pages 1-3 regarding the events involved in the production of an inflammatory response, and stated that there "is no guidance provided to detect agents that reduce inflammation by pathways **other than those disclosed.**"[14] The corollary of this statement is that there **is** sufficient guidance with respect to the inflammation pathways disclosed in the Specification. In view of this, Applicant has added new Claims 157-159 that are directed to the specific inflammation pathways referred to by the Examiner, *i.e.*, leukocyte adhesion to endothelial cells (Claim 157), leukocyte transmigration in endothelial tissue (Claim 158), and leukocyte extravasation in endothelial tissue (Claim 159). Since the Examiner recognized that there is sufficient guidance regarding how to use these methods, new Claims 157-159 are enabled.

More particularly, referring to new Claim 157, the Specification enables "identifying said test agent as reducing adherence of leukocyte cells to endothelial cells that express said carboxylated glycan" by substituting the Specification's exemplary agent antibody mAbGB3.1 with any test agent of interest in the exemplary methods discussed in Figure 10 on page 12, lines 17-25, the paragraph bridging pages 8-9, paragraph bridging pages 55-56, page 77, lines 1-16, Example 9 beginning on page 95, and Example 10 on page 98, lines 17-27.

Referring to new Claim 158, "identifying said test agent as reducing transmigration of leukocyte cells in endothelial tissue that comprises endothelial cells expressing said carboxylated

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[13] Specification, page 98, lines 5-9.
[14] (Emphasis added) *Id.*

glycan" is enabled by substituting any test agent of interest with the Specification's exemplary agent antibody mAbGB3.1 as described at page 56, lines 11-17, and page 98, line 27 to page 99, line 2.

With regard to new Claim 159, one of skill in the art is enabled to identify the "test agent as reducing extravasation of leukocytes cells in endothelial tissue that comprises endothelial cells expressing said carboxylated glycan" by replacing the Specification's exemplary agent antibody mAbGB3.1 with any test agent of interest as described in the paragraph bridging pages 68-69, in Example 10 beginning on page 96, and in Example 34 beginning on page 129.

From the above, new Claims 157-159 are enabled.

B. Cancer Cells

The Examiner recognized that the "the disclosure provides guidance for the identification of an agent which reduces inflammation or **cancer cell growth** related to the binding of the proteins annexin I, S100A8/A9 and amphoterin."[15] In view of this, Applicant has added Claim 161 to recite that the "carboxylated glycan binds to a molecule comprising one or more of S100A8, S100A9, S10012, amphoterin, annexin I, and amino acids 1 to 12 of annexin I." New Claim 161 is enabled as stated by the Examiner.

Regarding the recitation of "cancer" in rejected Claim 136, Applicant notes that this recitation has been cancelled from Claim 136 and instead introduced into new Claim 160. To expedite prosecution, Applicant comments as follows on the Examiner's grounds for rejecting Claim 136 as they arguably may apply to new Claim 160. In particular, the Examiner cited Zips *et al.* in support of the argument that "the state of the prior art indicates that the identification of an agent that reduces cancer in vitro does not adequately predict the effect of the drug when used to treat a cancer patient in vivo."[16] This ignores the **solution** to this problem that Zips *et al.* advanced at the end of the paragraph that was cited by the Examiner, *i.e.*, that "further evaluation in animal tumor systems is essential."[17]

The Examiner undermined the value of this solution by opining that "one would thus be required to screen a test agent in vivo to identify such an agent as reducing cancer, requiring

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15 (Emphasis added) Office Action, page 5, 2nd paragraph.
16 Office Action page 5, 2nd paragraph.
17 Zips *et al.*, page 3, 3rd paragraph, last sentence.

undue experimentation for one of ordinary skill in the art to use the invention as claimed."[18] This position misapplies the law.

> "The key word is 'undue' not 'experimentation.'"[19] "It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification."[20]

The Examiner appears to take the position that enablement is defeated because of the mere fact that *in vivo* experiments may be needed to determine the effect of an agent on cancer cell growth. This is inaccurate. What is important in the enablement inquiry is not whether *in vivo* experiments may be needed, but whether *in vivo* experiments require undue experimentation.

Indeed, Zips *et al.* contradicts the Examiner's position with respect to both the quality and quantity of experimentation. For example, with respect to the **quality** of available *in vivo* testing, Zips *et al.* teaches that *in vivo* methods are standardized and well established:

> "**Standardized, well-established** *in vitro* and ***in vivo*** methods are available for experimental evaluation of new anticancer agents."[21] "Over many decades, researchers in experimental tumor therapy have developed **well-proven, reliable** *in vitro* and ***in vivo*** methods to evaluate treatment response."[22]

With respect to the **quantity** of experimentation, Zips *et al.* teaches that

> "For evaluation of new anticancer agents, we advocate *in vitro* and ***in vivo*** experiments with at least two or three different tumor cell lines, applying functional non-clonogenic and, if applicable, clonogenic assays."[23]

This quantity of experimentation advocated by Zips *et al.* cannot be characterized as undue since it uses only 2-3 cell lines and known functional methods (clonogenic and non-clonogenic assays) that are further described in Zips *et al.*

Applicant notes that although Zips *et al.* discloses that "The use of these standardized experimental methods is time-consuming and costly,"[24] the law nonetheless is clear that the time

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18 Office Action, page 5, 2nd paragraph.
19 *In re Wands*, 8 USPQ2d 1404 (CAFC 1988), citing *In re Angstadt*, 537 F.2d at 504, 190 USPQ at 219 (CCPA 1976)
20 *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1329 (Fed. Cir. 1990).
21 Zips *et al.*, Abstract, and page 6, 1st column, last paragraph.
22 Zips *et al.*, page 1, 2nd column, 1st paragraph.
23 Zips *et al.*, page 6, 2nd column, 1st paragraph.
24 *Id.*

and cost of studies do not constitute undue experimentation if the methods are routine in the art.[25]

Furthermore, Zips *et al.* teaches **solutions** that reduce both the **time and cost** involved. For example, Zips *et al.* teaches using the tumor-excising assay which is "an alternative to this **time consuming** [tumor control assay] procedure" and which is "**less expensive** than the tumor control assay because no follow-up is necessary and the number of animals required is smaller."[26] In view of the above, test agents may be evaluated for their effect on cancer cell growth using "standardized, well-established," "well-proven, reliable," "well-characterized tumor models" *in vitro* and *in vivo* methods. Accordingly, new Claim 160 is enabled.

C. Neuron Cells

Newly added Claim 162 recites "identifying said test agent as reducing growth of neuron cells that express said carboxylated glycan." Enabling support is found in the Specification in, for example, the description of Figures 25-27 from page 17, line 6 to page 18, line 4, and Example 33 beginning on page 127, which discusses the effects of the exemplary antibody mAbGB3.1 agent in neuron outgrowth assays, as also shown in Figures 25-27. Since any test agent of interest may be substituted for the exemplary antibody mAbGB3.1 agent, then new Claim 162 is enabled.

Based on the above, Applicant respectfully requests withdrawal of the rejection of Claim 136 under 35 U.S.C. § 112, first paragraph, and avers that new Claims 156-162 are enabled.

5. REJECTION OF CLAIMS 123-128, 130, 131, 133 AND 134 UNDER 35 U.S.C. § 102(b) OVER VARKI *et al.*

The Examiner rejected Claims 123-128, 130, 131, 133 and 134 under 35 U.S.C. § 102(b) for alleged anticipation by Varki ***et al.***, U.S. Patent No. 5,5449,781.[27] Applicant respectfully disagrees because Varki *et al.* does not disclose all the elements of the claims as discussed below.

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25 *United States v. Telectornics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988).
26 (Emphasis added) Zips *et al.*, page 5, 2nd column, last full paragraph.
27 Office Action, page 6, item 12.

A. Claims 123-128 and new Claims 163-164

The Examiner admitted on three occasions that "Varki does not specifically teach that the BAP-glycan conjugate has 1-2 negative charges per molecule."[28] This is not the only deficiency of Varki *et al.* because it does not teach Claim 123's limitation in step d) of "**isolating** said first anionic BAP-glycan conjugate having from 1 to 2 negative charges per molecule." Nor does Varki *et al.* teach new Claims 163-164's limitation that the **"isolated"** first anionic BAP-glycan conjugate in step d) has **"1 negative charge** per molecule."

More particularly, Applicant notes that the method of Varki *et al.* produces BAP-glycan conjugates that contain a **mixture** of charges. Varki *et al.* does not disclose isolating conjugates that have from 1 to 2, or 1, negative charge per molecule from this mixture.

As demonstrated by the instant Specification, Figure 1[29] shows that treatment of BAP-coupled anionic bovine lung glycans of moderate negative charge with multiple exoglycosidases resulted in a **mixture** of conjugates containing neutral conjugates as well as those containing sulfate (S-1) and two sulfates (S-2). The conjugates containing different charges were further resolved by the inventors by HPLC and (Figure 1A) and reverse phase HPLC (Figure 1B) demonstrating that only a particular fraction of the mixture contained the recited **"from 1 to 2"** and **"1"** negative charges per molecule. In contrast, Varki *et al.*'s methods were directed **not** to **"isolating"** the conjugates based on whether they contained the recited "1 to 2 negative charges per molecule," but rather based on **size** for **sequence** analysis. For example, Varki *et al.* says that "when combined with specific exoglycosidase digestion, this can further facilitate **sequencing**."[30]

Applicant notes that Varki *et al.* discloses that "subsequent separation of the complexes into individual species is possible based upon the properties of the oligosaccharide (*e.g.*, charged complexes could be separated by ion exchange chromatography or iso-electric focusing.)."[31] Importantly, however, this statement does not teach that, even when separated based on charge, that the artisan aim at **"isolating"** from the mixture those complexes that contain the specifically recited numerical **"from 1 to 2"** or **"1"** negative charges per molecule.

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28 Office Action, page 8, 1st paragraph, page 11, item 19, and page 16.
29 Specification, page 10, lines 22-28.
30 Varki *et al.*, column 11, lines 13-15.
31 Varki *et al.*, column 11, lines 53-60.

Applicant notes that the Examiner attempted to overestimate Varki *et al.*'s deficient disclosure by stating that Varki *et al.*'s "process **may** use a number of conjugates that would inherently have the claimed charges."[32] This misapplies the law under inherency, which says that:

> "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing **may** result from a given set of circumstances is not sufficient."[33]

Therefore, the Examiner's statement that Varki *et al.* "**may** use a number of conjugates that would inherently have the claimed charges" is not sufficient for inherency.

From the above, Varki *et al.* fails to disclose "**isolating** said first anionic BAP-glycan conjugate having from **1 to 2** negative charges per molecule," which is recited in each of rejected Claims 123-128.

With respect to new Claims 163-164, Varki *et al.* does not disclose "**isolating**" a BAP-glycan conjugate that has "**1** negative charge per molecule."

B. Claims 130-131 and 133-134, and New Claims 165-166

The Examiner asserted that Varki *et al.*'s method comprises "isolating from the molecule a first anionic glycans containing from 1-4 charges; desialylating the isolated first anionic glycans to produce a desialylated anionic glycans containing from 1-4 negative charges; and isolating from the first glycans a second anionic glycans containing from 1-4 negative charges."[34] This bold assertion is **unsupported** by any of Varki *et al.*'s disclosure that the Examiner referred to. In particular, nowhere does Varki *et al.* specifically teach "isolating" the recited range of "**from 1 to 4**" in Claims 130-131 and 133-134, and the range of "**from 1 to 3**" in new Claims 165-166.

From the above, Varki *et al.* fails to disclose all the elements of rejected Claims 130-131 and 133-134, and new Claims 163-164.

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32 (Emphasis added) Office Action, page 8, 1st paragraph.

33 (Emphasis added) *In re Robertson*, 49 USPQ2d 1949, 1950 (Fed. Cir. 1999), citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578, 581, 212 USPPQ 323, 326 (CCPA 1981); see also, *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047, 34 USPQ2d 1565, 1567 (Fed. Cir. 1995), rehearing denied, in banc suggestion declined (Jun 21, 1995).

34 Office Action, page 8, 1st paragraph.

Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 123-128, 130-131, 133-134 under 35 U.S.C. § 102(b) for alleged anticipation by Varki *et al.*, and asserts that new Claims 163-166 are novel.

6. REJECTION OF CLAIMS 123-128, 130-135, 137, 138, 140 AND 141 UNDER 35 U.S.C. § 103(a) OVER VARKI *et al.*, SCHMIDT *et al.* AND HODGES *et al.*

The Examiner rejected Claims 123-128, 130-135, 137, 138, 140 and 141 under 35 U.S.C. § 103(a) for allegedly being obvious over Varki *et al.* (U.S. Patent No. 5,5449,781) in view of Schmidt *et al.* (Biochimica et Biophysica Acta (2000) 1498:99-111) and Hodges *et al.* (U.S. Patent No. 5,738,996).[35] Applicant respectfully traverses because a *prima facie* case of obviousness has not been established.

A *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) discloses all the elements of the claimed invention, (b) provides one of skill in the art with incentives or reasons to combine the claim elements to yield the claimed combination,[36] and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish **any one** of these three requirements precludes a finding of a *prima facie* case and, without more, entitles Applicant to withdrawal of the rejection.[37] Applicant urges that the Examiner has failed to establish, not one, but all three requirements, thus entitling Applicant to withdrawal of this rejection.

A. The Claims' Elements Are Not Taught By the References

The Examiner is respectfully reminded that **"all** the claim limitations **must** be taught or suggested by the prior art."[38] This is not the case. The Examiner took the position that "a method for purifying a carboxylated glycans comprising **nearly all** of the claimed elements was known, as taught by Varki."[39] This misapplies the law which requires that "all," not "nearly all" as asserted by the Examiner, the claim limitations "must" be taught by the cited references.

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35 Office Action, page 9, item 18.

36 *KSR International Co. v. Teleflex Inc.*, 127 s. Ct. 1727, 82 USPQ2nd 1385 (2006).

37 MPEP '2143; *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

38 (Emphasis added) MPEP 2143.03, citing *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

39 (Emphasis added) Office Action, page 13, item 22.

Since the Examiner used an improper basis for the rejection, this element of a *prima facie* case of obviousness is not made with respect to any of the rejected claims.

The rejection is further discussed below with reference to two grouping of the claims.

1. **Rejected Claims 123-128, 135, 137-138, and 140-141, and New Claims 151-164**

Regarding rejected Claims 123-128, 135, 137-138, and 140-141, and new Claims 151-164, Applicant incorporates the above discussion in item 5.A, beginning on page 18, with respect to the deficiency of Varki *et al.*'s disclosure, namely that Varki *et al.* does not disclose, either expressly or under the doctrine of inherency, Claim 123's limitation in step d) of "**isolating** said first anionic BAP-glycan conjugate having **from 1 to 2 negative charges** per molecule." Indeed, the Examiner recognized this deficiency by three times stating that "Varki does not specifically teach that the BAP-glycan conjugate has 1-2 negative charges per molecule."[40] Varki *et al.* also does not disclose new Claims 163-164's limitation that the **"isolated"** first anionic BAP-glycan conjugate in step d) has "**1 negative charge** per molecule."

Hodges *et al.* and Schmidt *et al.* do not cure this deficiency because nowhere do they make reference to any BAP-glycan conjugates, let alone the specifically recited range of "from 1 to 2" and "1" negative charges on those conjugates. Therefore, this element of a *prima facie* case of obviousness is lacking with respect to rejected Claims 123-128, 135, 137-138, and 140-141, and new Claims 151-164.

Moreover, with respect to Claim 135 and new dependent Claim 151-162, none of the cited references discloses the limitation of step a)ii) that an the specific binding of the antibody to the carboxylated glycans "is not reduced by a carboxylate-neutralized glycan." This is an additional reason why this element of a *prima facie* case of obviousness is lacking with respect to Claim 135 and new dependent Claim 151-162.

Also, none of the references discloses the following additional limitations in new Claims 151-162, namely that "the antibody does not specifically bind to one or more acid selected from the group consisting of glucuronic acid, galacturonic acid, sialic acid, lactic acid, pyruvic acid, and uronic acid" (Claim 151), "the antibody does not specifically bind to one or more sulfated glycan selected from the group consisting of thyroglobulin and neural cell adhesion molecule"

[40] Office Action, page 8, 1st paragraph, page 11, item 19, and page 16.

(Claim 152), "the antibody does not specifically bind to one or more glycosaminoglycan selected from the group consisting of chondrosamine, chondroitin sulfate, chondroitin sulfate tetramer, chondroitin sulfate octamer, hyaluronic acid tetramer, hyaluronic acid octamer, heparin, and heparin sulfate" (Claim 153), "the antibody does not specifically bind to one or more phosphorylated sugar selected from the group consisting of glucose-1-phosphate, glucose-6-phosphate, mannose-6-phosphate, and galactose-6-phosphate" (Claim 154), "the antibody does not specifically bind to one or more sulfated sugar selected from the group consisting of glucose-6-sulfate and galactose-6-sulfate" (Claim 155), the "carboxylated glycan that is expressed by said endothelial cells binds to a molecule comprising one or more of S100A8, S100A9, S10012, amphoterin, annexin I, and amino acids 1 to 12 of annexin I" (Claim 156), "identifying said test agent as reducing adherence of leukocyte cells to endothelial cells that express said carboxylated glycan" (Claim 157), "identifying said test agent as reducing transmigration of leukocyte cells in endothelial tissue that comprises endothelial cells expressing said carboxylated glycan" (Claim 158), "identifying said test agent as reducing extravasation of leukocytes cells in endothelial tissue that comprises endothelial cells expressing said carboxylated glycan" (Claim 159), "identifying said test agent as reducing growth of cancer cells that express said carboxylated glycan" (Claim 160), the "carboxylated glycan that is expressed by said cancer cells binds to a molecule comprising one or more of S100A8, S100A9, S10012, amphoterin, annexin I, and amino acids 1 to 12 of annexin I" (Claim 161), and "identifying said test agent as reducing growth of neuron cells that express said carboxylated glycans" (Claim 162). Therefore, this is yet another reason why this element of a *prima facie* case of obviousness remains lacking with respect to new Claims 151-162.

2. Rejected Claims 130-134, and New Claims 165-166

Applicant incorporates by reference the above discussion in item 5.B., beginning on page 19, with respect to Varki *et al.*'s failure to teach "**isolating**" an anionic glycan containing the recited range of "**from 1 to 4**" (rejected Claims 130-134), and "**from 1 to 3**" (new Claims 165-166) negative charges per molecule.

Hodges *et al.* and Schmidt *et al.* also do not provide what is missing from Varki *et al.* because neither reference anywhere discloses the specifically recited range of "**from 1 to 4**"

(rejected Claims 130-134) and the range of "**from 1 to 3**" (new Claims 165-166) negative charges on those conjugates.

Because the combined references do not disclose all the limitations of the claims, this **alone** negates a *prima facie* case of obviousness and entitle Applicant to withdrawal of the rejection.

B. There Is No Incentive to Combine The References

A key requirement for a *prima facie* case of obviousness is whether the prior art provides a person of ordinary skill with a reason or incentive to modify the reference to arrive at the claimed invention.[41] In particular,

> "the examiner must show *reasons* that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would *select* the elements from the cited prior art references for *combination in the manner claimed*."[42] To find a claim obvious, there must be "a reason or suggestion (explicit or implicit) in the art for combining the art as proposed."[43] Evidence of a suggestion, teaching, or motivation to modify prior art references "must be *clear and particular*."[44] The Patent Office "... cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but *must set forth the rationale* on which it relies."[45]

The Examiner's attention is respectfully drawn to the fact that the invention is premised, in part, on the inventors' **discovery** that carboxylated glycans are expressed on endothelial cells,[46] that leukocytes specifically bind to the carboxylated glycans that are expressed on endothelial cells,[47] that this specific binding mediates leukocyte adhesion to endothelial cells,[48]

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41 *KSR International Co. v. Teleflex Inc.*, 127 s. Ct. 1727, 82 USPQ2nd 1385 (2006), *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598-99 (Fed. Cir. 1988) and *In re Jones*, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992).

42 (Emphasis added) *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *See, also, Robotic Vision Systems Inc. v. View Engineering Inc.*, 51 USPQ2d 1948 (Fed. Cir. 1999); *Sibia Neurosciences v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000); *In re Oetiker*, 977 F.2d 1443, 1448 (Fed. Cir. 1992).

43 *Sibia Neurosciences v. Cadus Pharmaceutical Corp.*, 225 F.3d 1349, 1355-56 (Fed. Cir. 2000); *In re Oetiker*, 977 F.2d 1443, 1448 (Fed. Cir. 1992).

44 (Emphasis added) *In re Dembiczak*, 175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999), *citing C.R. Bard*, 157 F.3d 1340 at 1352, 48 USPQ2d at 1232. See, also, *In re Sang Su Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002).

45 (Emphasis added).

46 Specification, page 91, lines 3-16.

47 Specification, page 12, describing Figures 7-10, page 14 describing Figures 14 and 16.

leukocyte transmigration in endothelial tissue,[49] and leukocyte extravasation in endothelial tissue,[50] that the carboxylated glycans are expressed on tumor cells and promote their growth,[51] and that carboxylated glycans are expressed on neuron cells and promote their growth.[52] In recognition of the importance of the carboxylated glycans, the inventors sought to purify them by enriching for glycans molecules that have a **particular range** of negative charge, namely from 1 to 2 negative charges (rejected Claims 123-128, 135, 137-138 and 140-141) and from 1 to 4 negative charges (rejected Claims 130-134). Until the inventors' discovery, the prior art **did not know** of the role of carboxylated glycans that have a **particular range** of negative charges in any of the above-discussed biological phenomena. Thus, analyzing the impact of the cited reference must be made with the art's ignorance in mind.

The Examiner argued that "Varki teaches that it would be desirable to use the methods to screen for proteins which bind to the saccharides and that the methods enable the production of antibodies specific for the saccharides."[53] One thing that this argument ignores is that the limitation of **"isolating"** molecules having from 1 to 2 negative charges (rejected Claims 123-128, 135, 137-138 and 140-141) and from 1 to 4 negative charges (rejected Claims 130-134) was **not known** in the art. The law is clear that obviousness cannot be predicated on what is unknown.[54]

Moreover, Varki *et al.* **teaches away from selecting** the specifically recited ranges of negative charges. Varki *et al.*'s methods are directed to purifying carbohydrate antigens to raise antibodies. The problem faced by Varki *et al.* was that contaminating monosaccharides interfered with the targeted oligosaccharides. Varki *et al.* solved this problem by treating the mixture with exoglycosidase digestion to "further facilitate sequencing" by shifting the position

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48 Specification, legend of Figure 10 on page 12, lines 17-25, the legend of Figure 17 on page 15, the paragraph bridging pages 8-9, paragraph bridging pages 55-56, page 77, lines 1-16, Example 9 beginning on page 95, and Example 10 on page 98, lines 17-27.

49 Specification, page 56, lines 11-17, page 98, line 27 to page 99, line 2.

50 Specification, paragraph bridging pages 68-69, in Example 10 beginning on page 96, and in Example 34 beginning on page 129.

51 Specification, Figure 23 legend, page 16, lines 6-21, page 78, lines 6-10, and Example 28, page 123, lines 14-21.

52 Specification, Figures 25-27, from page 17, line 6 to page 18, line 4, and Example 33 beginning on page 127, which discusses the effects of exemplary agents in neuron outgrowth assays, as also shown in Figures 25-27.

53 Office Action, page 13, item 22.

54 *In re Newell*, 891 F.2d 899, 901,13 USPQ2d 1248, 1250 (Fed. Cir.1989). Accord, *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

of the monosaccharides on reverse phase HPLC based on **size**, not charge.[55] Thus, if Varki *et al.* provided an incentive, it is toward size separation, **and away from** a separation based on the specifically recited range of from 1 to 2 (rejected Claim 123-128, 135, 137-138, 140-141 and new Claims 151-164) and from 1 to 4 (rejected Claims 130-134 and new Claims 165-166) negative charges per molecule.

With respect to each of the new Claims 151-162, the art **did not know** of the role of carboxylated glycans in the above-discussed biological phenomena, and so could not provide an incentive to combine the steps that are recited in each of these claims.

Thus, this element of a *prima facie* case of obviousness remains lacking. This alone warrants withdrawal of the rejection based on obviousness.

C. There Is No Reasonable Expectation of Success

The Examiner is respectfully reminded that

> ". . . a reasonable expectation of success is necessary" to establish a *prima facie* case of obviousness.[56] "[T] the reasonable expectation of success must be founded in the prior art, **not** in the applicant's disclosure."[57]

The Examiner argued in favor of this element "because Varki teaches all of the required elements."[58] This is wrong, as discussed above, because Varki fails to teach the recited range of negative charges.

The Examiner also argued that a reasonable expectation of success is present because "Hodges teaches simplified screening methods."[59] However, this is not probative because "routine experimentation" does not negate patentability. The court has expressly stated that

> "[W]e do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negatived by the manner in which the invention was made.'"[60]

Therefore, the Examiner has failed to establish a reasonable expectation of success in combining the recited method steps.

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55 Varki *et al.*, column 11, lines 13-26.

56 *In re Clinton*, 527 F.2d 1226, 1228, 188 USPQ 365, 367 (CCPA 1976); See also *Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).

57 *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988) as cited in *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

58 Office Action, page 13, item 22.

59 Office Action, page 13, item 22.

60 *In re Fay and Fox*, 146 USPQ 47, 51 (CCPA 1965).

In view of the above, not one, but each of the three elements of obviousness has not been established. Accordingly, Applicant respectfully requests withdrawal of the rejection of Claims 123-128, 130-135, 137-138, and 140-141 under 35 U.S.C. § 103(a).

7. REJECTION OF CLAIMS 123-135 AND 137-141 UNDER 35 U.S.C. § 103(a) OVER VARKI *et al.*, HODGES *et al.* AND SCHMIDT *et al.*

The Examiner rejected Claims 123-135 and 137-141 under 35 U.S.C. § 103(a) for allegedly being obvious over Varki *et al.* (U.S. Patent No. 5,5449,781) in view of Hodges *et al.* (U.S. Patent No. 5,738,996) and Schmidt *et al.* (Biochimica et Biophysica Acta (2000) 1498:99-111).[61] Applicant respectfully disagrees because none of the three mandatory elements of a *prima facie* case of obviousness has been established.

A. The References Fail to Disclose All the Limitations Of the Claims

Applicant incorporates by reference the arguments above under item 6.A., beginning on page 20. With respect to rejected Claims 123-129, 135 and 137-141, Applicant additionally incorporates the above arguments in item 6.A.1. Regarding rejected Claims 130-134, Applicant also incorporates the above arguments in item 6.A.2.

Applicant also notes the Examiner's additional admission that "neither Varki nor Hodges teaches that the molecule comprising the glycans is a glycoprotein such as RAGE."[62] The Examiner attempted to overcome this deficiency by stating that Schmidt *et al.* teaches RAGE.[63] However, RAGE is recited only in Claim 129. Thus, Schmidt *et al.*'s disclosure of RAGE still does not cure the above-discussed deficiency with respect to **each** of the rejected claims (including Claim 129) regarding the recited range of from "1 to 2" and from "1 to 4" negative charges per molecule.

The deficiency of this requisite element of a *prima facie* case of obviousness mandates withdrawal of the rejection based on alleged obviousness.

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61 Office Action, page 13, item 23.
62 Office Action, page 17, item 25.
63 Office Action, page 17, item 27.

B. An Incentive To Combine The References Is Absent

Applicant incorporates the above discussion in item 6.B., beginning on page 23, and further advances the following comments.

The Examiner provided one argument in support of an incentive to combine the references, namely that "one of ordinary skill in the art would have been motivated to combine these teachings because Varki teaches that it would be desirable to produce BAP conjugates with glycoproteins as well as oligosaccharides."[64] However, the Examiner is respectfully reminded that the incentive must be directed to the **claimed combination** of elements. Importantly, the claims are not directed to methods for purifying a BAP conjugate with a glycoprotein or polysaccharide, but rather to purifying anionic BAP glycan conjugates **"having from 1 to 2"** (rejected Claims 123-129, 135, and 137-141) or **"having from 1 to 4"** (rejected Claims 130-134) negative charges per molecule. Because the cited references did not teach these particular ranges, there was **no reason or incentive for the artisan to select them.** Obviousness cannot be predicated on what is unknown.[65]

Because this prong of a *prima facie* case of obviousness is not established, a *prima facie* case of obviousness cannot stand. This necessitates withdrawal of the rejection based on alleged obviousness.

C. There is No Reasonable Expectation Of Success

Applicant incorporates by reference the above arguments under item 6.C., beginning on page 25. Applicant also adds the following comments.

The Examiner argued that "one of ordinary skill in the art would have had a reasonable expectation of success in combining these teachings because Varki teaches that the process may be used to purify any molecule with a bound glycan, such are RAGE."[66] But the availability of known methods does not negate patentability. The court has expressly stated that

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64 Office Action, page 17, item 28.

65 *In re Newell*, 891 F.2d 899, 901,13 USPQ2d 1248, 1250 (Fed. Cir.1989). Accord, *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

66 Office Action, page 17, item 28.

> "we do not agree that 'routine experimentation' negatives patentability. The last sentence of section 103 states that 'patentability shall not be negatived by the manner in which the invention was made.'"[67]

Therefore, Varki *et al.*'s statement does not provide the requisite reasonable expectation of success in combining the claimed method steps.

The Examiner also argued that "RAGE was a known protein at the time of the invention. The discovery that a previously [known] protein has previously unknown elements (e.g. bound glycans) does not render the use of that protein with a known method novel."[68] Applicant is unaware of any case law that would colorably support this assertion, and respectfully invites the Examiner to cite it for Applicant's consideration.

From the above, a reasonable expectation of success in practicing to claimed combination of steps has not been made. Therefore, a *prima facie* case of obviousness is defective.

Since the Examiner has failed to establish not just one, but each of the three, elements of a *prima facie* case of obviousness, Applicant respectfully requests withdrawal of the rejection of Claims 123-135 and 137-141 under 35 U.S.C. § 103(a) over Varki *et al.*, Hodges *et al.*, and Schmidt *et al.*

CONCLUSION

All grounds of objection and rejection of the Office Action having been addressed, Applicant respectfully requests reconsideration of the application.

Dated: January 28, 2008

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67 *In re Fay and Fox*, 146 USPQ 47, 51 (CCPA 1965), *In re Saether*, 492 F.2d 849, 181 USPQ 36 (CCPA 1974).

68 Office Action, page 17, item 28.